

# Prevalence and Risk Factors for Barrett's Esophagus in Patients with GERD in Northern India; Do Methylene Blue-directed Biopsies Improve Detection of Barrett's Esophagus Compared the Conventional Method?

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## ABSTRACT

### BACKGROUND

The reported rates of Barrett's esophagus (BE) ranged from 2.6% to 23% in Indian patients with gastro-esophageal reflux disease (GERD) symptoms. The role of methylene blue chromoendoscopy during endoscopy, either for the diagnosis of Barrett's esophagus or for the detection of dysplasia and early cancer, remains controversial.

AIM: Our study was designed to find out the endoscopic as well as histological prevalence of BE in India in a specified patient population affected by GERD, and whether methylene blue chromoendoscopy improves detection of specialized intestinal metaplasia in endoscopically suspected Barrett's esophagus in GERD patients.

### METHODS

Three hundred and seventy eight patients with characteristic symptoms of GERD from Northern India were subjected to upper endoscopy. On endoscopic suspicion of columnar lined epithelium (CLE) either 4-quadrant conventional biopsies at 2 cm interval or Methylene Blue (MB) directed biopsies were obtained randomly. The two groups were compared for the detection of Specialized Intestinal Metaplasia (SIM), which was diagnosed if the intestinal goblet cells were present.

### RESULTS

Out of 378 patients with GERD, 56 (14.81%) were suspected of CLE on endoscopy. After taking biopsy samples from the 56 patients, only 9 (2.38%) had specialized intestinal metaplasia on histopathological examination. Five (15.15%) patients in the conventional group and four (17.39%) patients in the chromoendoscopy group ( $p=0.55$ ) were diagnosed as having BE. On univariate analysis the predictors of SIM were symptoms of reflux and length of CLE.

### CONCLUSION

The prevalence of biopsy proven BE and CLE in Northern India was 2.38% and 14.81%, respectively in patients with symptoms of GERD. The results of MB directed biopsies were similar to conventional biopsies in detecting SIM.

### KEYWORDS

Barrets; Adenocarcinoma; Ulcer; Esophagus

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic disease that is associated with a range of troublesome symptoms such as heartburn and regurgitation or complications such as erosive esophagitis which can in turn have a significant impact on health-related quality of life and work productivity.<sup>1-4</sup> GERD symptoms occur at least once a month in 44%, once a week in 20%, and daily in 7% of the adult US population.<sup>5-7</sup>

The epidemiological studies of GERD in India are sparse. In a questionnaire-based study, Bhatia and colleagues reported a weekly prevalence of GERD symptoms in 7.6% of the Indian population.<sup>8</sup> Other questionnaire-based cross-sectional studies by Sharma et al.<sup>9</sup> and Kumar et al.<sup>10</sup> showed prevalence rates of 16.2% to 18.7% for GERD in the Indian population. These studies emphasize that the prevalence of GERD in India is likely to be between 8% and 19%, which is comparable to the prevalence rates in western countries.

Barrett's Esophagus (BE) is found in 1.6% of the general population and in 10% of those patients who undergo endoscopy for symptoms. Although the prevalence of gastroesophageal reflux is increasing in Asia, the prevalence of BE and esophageal adenocarcinoma (EAC) have so far remained low in most Asian countries.

The American College of Gastroenterology (ACG) defines BE as endoscopically recognizable columnar metaplasia of the esophagus, which is confirmed to have intestinal metaplasia (i.e. goblet cells) in mucosal biopsy specimens.<sup>11</sup> On H&E staining, goblet cells have a distended lateral border, compressed basal nucleus and basophilic apical cytoplasm. Goblet cells have mucins and stain intensely with Alcian blue at pH 2.5.<sup>12</sup>

The prevalence of BE in Asia outside Japan ranges from 0.06% to 6.2%. In Japan, the prevalence of BE is reportedly 19.9% in a series where biopsy was employed<sup>13</sup> and as high as 43% in those series without biopsy.<sup>14</sup> Till date, few studies from India have reported a prevalence rate of BE ranging from 2.6% to 23%.<sup>15-17</sup>

Methylene blue is a vital stain that is readily taken up by absorptive epithelium, primarily that of the small bowel and colon, but not by normal squamous or gastric epithelium. Most chromoendoscopic studies in BE have evaluated the role of methylene blue. However, the use of this agent, either for the diagnosis of Barrett's metaplasia or for the detection of Barrett's dysplasia and early cancer, remains controversial because of a wide range of reported diagnostic sensitivities (32%-98%) and specificities (23%-100%).<sup>18-26</sup> Two of 3 randomized, controlled, cross-over trials showed an increased yield in the diagnosis of BE with MB-directed biopsies compared with random biopsies.<sup>22,24</sup>

Contrary to previous beliefs, the prevalence of GERD in India is higher than previously estimated and appears to be similar to that of the western countries.<sup>27</sup> Although patients with GERD are at a higher risk for BE,<sup>10</sup> it is seen that the prevalence of BE is low in India. However, with the new findings regarding the high prevalence of GERD in India, there is a renewed interest in revisiting the prevalence of complications of GERD such as BE.

We aimed to assess the prevalence of BE in India in an era when the prevalence of GERD has been reported to be increasing. Few studies have been carried out in India to estimate the prevalence of BE with reported rates ranging from 2.6% to 23%.<sup>16,28,29</sup> The prevalence of CLE in Asia is reported to be 5-7% for short segment and 1-3.4% for long segment.<sup>30,31</sup> And not all patients with CLE are subsequently found to have BE on histological examination (i.e. specialized intestinal metaplasia). Therefore, we also aimed to find out whether MB-directed biopsies would improve the detection of BE in endoscopically suspected CLE as compared with conventional biopsies.

## MATERIALS AND METHODS

### DEFINITIONS

Patients fulfilling inclusion criterion were subjected to endoscopy with an Olympus GIF-Q180 videoendoscope (Olympus Co. Tokyo, Japan) after induction of oropharyngeal anaesthesia with 10% lidocaine spray. The gastroesophageal junction

(GEJ) was defined as the “pinch” at the distal end of the esophagus, coinciding with the most proximal margin of the gastric folds. Endoscopic esophagitis (esophageal mucosal breaks), if present, were graded according to the Los Angeles classification system. The CLE was described as endoscopic findings consistent with BE that awaited histological evaluation. CLE was identified as columnar epithelium above gastroesophageal junction which had a reddish color and a velvety texture which could be distinguished easily from normal pale and glossy esophageal squamous epithelium.

The length of CLE was estimated by subtracting the distance from incisors to the squamocolumnar junction (Z-line) from the distance from incisors to the gastroesophageal junction. Patients were classified into short-segment BE (SSBE) if the length of columnar appearing mucosa was less than 3 cm above the gastroesophageal junction and long-segment BE (LSBE) if the length of columnar mucosa was equal to or more than 3 cm.

#### ENDOSCOPY

Patients with characteristic symptoms of GERD were subjected to upper endoscopy using the conventional method. The appearance and location of the squamocolumnar junction, location of GEJ, the presence or absence of hiatus hernia, endoscopic esophagitis and the presence or absence of columnar lined esophagus, its length and morphological types were carefully evaluated, identified and the findings were recorded. On endoscopic suspicion of BE either conventional biopsies or MB-directed biopsies were obtained randomly.

In the first group of patients, the biopsy specimens were obtained conventionally in a 4-quadrant fashion at intervals of 2 cm from the circumferential endoscopic Barrett's epithelium in the distal esophagus. In patients with small islands or irregular tongues of columnar appearing mucosa, at least two specimens were obtained within the abnormal-appearing mucosa at intervals of 1cm from the GEJ to the proximal extent of the abnormality. All biopsy specimens were obtained using standard biopsy forceps and placed in bottles containing 10%

of buffered formalin solution.

In the second group, chromoendoscopy was done with methylene blue (randomization) on columnar appearing mucosa with the help of a spray catheter (PW-5L, Olympus America, Inc., Melville, NY) for spraying reagents onto the CLE in the following order. First, the distal esophagus was washed with 10% acetylcysteine (Mucomyst) to dissolve the mucus layer and clear the esophagus of saliva and gastric secretions. The volume sprayed varied according to the length of ESEM (endoscopically suspected esophageal metaplasia), an average of 6 ml for short segment and 12 ml for long segment was used. Next, a 0.5% solution of MB was sprayed on the columnar-lined portion of the distal esophagus until dark blue staining was achieved. The volume of MB solution sufficient to cover the CLE was used (~5-20 ml). After 1 to 2 minutes, the distal esophagus was irrigated vigorously with tap water (30-100 ml) until there was no further loss of staining within the columnar mucosa. Positive staining was defined as blue staining that persisted despite vigorous washing. After MB staining, the mucosal pattern was classified as described by Canto et al.<sup>19</sup> into: diffuse pattern (at least 75% of columnar epithelium stained blue), non-diffuse pattern (less than 75% of columnar epithelium stained blue) and unstained (predominance of pink columnar epithelium). MB directed biopsy specimens were obtained from stained or heterogeneously stained mucosa. From unstained areas, random biopsy samples were taken from CLE and included in the group of patients in whom the biopsy samples were obtained in a conventional way.

#### HISTOPATHOLOGY

All biopsy specimens obtained either in the conventional way or after MB chromoendoscopy were stained with H&E in combination with alcian blue stain at pH 2.5. The specimens were examined for the presence of SIM, which was diagnosed if intestinal goblet cells were present in the columnar epithelium with blue staining.<sup>11</sup> The biopsy specimens were evaluated by pathologists, who were blinded to the method used to obtain the biopsy specimens

(MB-directed or conventional) and the status of MB staining (MB-stained or unstained specimen). The presence of dysplasia was assessed using the standard criteria and classified as no dysplasia, low-grade dysplasia, high-grade dysplasia, and adenocarcinoma according to the Vienna classification of epithelial neoplasia of the digestive tract.<sup>32</sup>

## STATISTICS

Statistical analyses were performed using statistical package for Social Sciences (SPSS), version 17.0 (Chicago, IL). Statistics were presented as mean±SD for continuously distributed variables and as frequency (%) for categorical variables. The prevalence of endoscopically suspected BE and that of biopsy-proven BE were calculated as percentage prevalence. Patients with biopsy-proven BE were compared with those in whom biopsy did not show evidence of BE. The two groups were compared using Student's t-test in case of continuously distributed variables and Chi-square and Fisher's exact tests in the case of categorical variables. Next, the predictors of biopsy-proven BE (SIM) were determined using logistic regression analysis with the presence of metaplasia as the dependent variable and a number of clinical and endoscopic variables as independent variables. A two-sided *p* value of <0.05 was considered as statistically significant.

This study was carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association in a tertiary care hospital in North India and approved by the medical ethics committee. Patients older than 25 years, with troublesome symptoms of GERD in the past 3 months were recruited from Northern India after obtaining written informed consent.

## RESULTS

**Patients with GERD:** A total of 378 GERD patients from January 2010 to February 2012 were recruited from five northern states of India. The mean±SD age of all patients with GERD was 48.15±10.90 years with a male/female ratio of 2:1. The mean±SD duration of symptoms before first

endoscopy was 7.43±1.62 months with heartburn being present in 47%, regurgitation in 32% and both symptoms in 21%. The patients were classified according to endoscopic findings into NERD (72%) and erosive GERD (28%). Among 107 patients who had features of mucosal injury on endoscopy, most of them (76%) had LA-Grade A, 18% had LA-Grade B, 4% had LA-Grade C, and 2% had LA-Grade D. 154 patients (41%) were found to have hiatus hernia with a mean±SD length of 3.26±1.04 cm and only 54% of them had varying grades of endoscopic esophagitis.

**Prevalence of CLE:** Of all GERD patients, only 56 had endoscopic suspicion of esophageal metaplasia yielding a prevalence of 14.81% of CLE in patients with GERD. On endoscopic examination of all 56 patients, 34% had circumferential CLE, 34% had tongue like extensions and 32% isolated islands. The mean±SD age of patients with CLE was 48.84±10.49, 80% of whom were men. The average duration of symptoms before an index endoscopy in patients with CLE was 8 months with heartburn being the most frequent symptom (57%), followed by regurgitation (32%), and both symptoms (10.7%). Forty patients (70%) were found to have normal endoscopy and 17 (30%) had erosive esophagitis. The short segment type of CLE was observed in 55% of the patients with a mean±SD length of 1.86±0.68 cm and the long segment in 12.5% with a mean±SD length of 3.43±0.49 cm.

**Prevalence of BE:** Histological examination of biopsies from 56 patients revealed SIM in 9 patients only, so the prevalence rate of SIM or histological BE was 2.38% in our study. The percentage of patients with CLE who had SIM on histological examination was 16.07% which was more frequently found in long segment CLE. The mean±SD age of patients with SIM was 52.55±8.34 years, 90% of whom were men. Regurgitation was the most common complaint followed by heart burn and both symptoms. Most patients (89%) had no evidence of erosive esophagitis even though hiatus hernia was observed in 77% of patients with a mean±SD length of 4.28±1.58 cm. Four patients were found to have long segment BE and two patients had short

segment BE. Histological esophagitis was observed in 22% of patients with BE and none had dysplasia.

**Methylene Blue vs Conventional Biopsy:** The patients with CLE (n=56) were randomly subjected to either conventional biopsies or MB directed biopsies. Out of 28 patients in the MB chromoendoscopy group, only 23 showed positive staining with MB and the remaining 5 patients with unstained columnar appearing mucosa were included in the conventional group. The mean±SD ages of patients in the conventional and chromoendoscopy groups were 47.9±10.6 and 50±10.53 years, respectively, with a male to female ratio of 4:1 ( $p>0.05$ ). The duration of symptoms between the two groups was also similar ( $p=0.69$ ). In both groups heartburn was the most common complaint followed by regurgitation and both symptoms ( $p=0.85$ ). The number of patients with erosive GERD and NERD in the two groups was also similar ( $p>0.05$ ). Hiatus hernia was seen in about half the patients in both groups ( $p=0.79$ ) with an average length of 3.4 cm ( $p=0.88$ ). Out of 33 patients in the conventional group, only 10 patients had erosive esophagitis in varying grades according to LA classification compared with 7 patients in the Chromoendoscopy group ( $p=0.93$ ). The percentage of patients with different morphological classes did not differ significantly in the two groups ( $p=0.49$ ). More patients in both groups had short segment CLE as compared with long segment CLE ( $p=0.68$ ). It was observed that the mean±SD number of biopsy samples per patient obtained using the conventional method was 4.12±1.76 which was significantly more compared with 3.0±0.80 obtained after MB chromoendoscopy to detect the same percentage of patients with SIM ( $p=0.002$ ). Also, the rate of detection of SIM in patients with CLE was similar in the two groups ( $p=0.55$ , table 1). However, the advantage of chromoendoscopy over conventional method was the fewer biopsies needed to detect the same proportion of patients.

The age ( $p=0.26$ ), the sex ( $p=0.65$ ), the symptom duration ( $p=0.46$ ), the hiatus hernia ( $p=0.17$ ) or its length ( $p=0.54$ ), esophagitis ( $p=0.25$ ) or its LA grades ( $p=0.47$ ), and the CLE class ( $p=0.75$ ) were not predictors of SIM; while the reflux symp-

**Table 1: Comparison of chromoendoscopy and conventional endoscopy in the detection of SIM**

Group	No. of patients with biopsy samples	SIM present	% SIM	*p value
Conventional	33	5	15.20	0.55
Chromoendoscopy	23	4	17.40	

\*p-value calculated by Pearson's Chi-square test

**Table 2: Predictors of SIM or Barrett's Esophagus**

Parameters	No metaplasia (n=47)	Metaplasia (n=9)	p value
Age (yrs) (mean±SD)	48.19 ±10.83	52.56 ±8.84	0.26
Male n(%)	37(78.7)	8(88.8)	0.67
Female n(%)	10(21.3)	1(11.1)	0.65
Symptom duration (mo) (mean±SD)	7.89 ±1.25	8.22 ±0.97	0.46
<b>Symptoms</b>			0.004
Heartburn n(%)	32(68.1)	1(11.1)	
Regurgitation n(%)	11(23.4)	6(66.7)	
Non-erosive GERD n(%)	31(66)	8(88.9)	0.34
Erosive GERD n(%)	16(34.0)	1(11.1)	0.25
Hiatus Hernia n(%)	24(51.1)	7(77.8)	0.17
Length of Hiatus hernia (mean±SD) cm	3.29±0.98	4.28 ±1.58	0.54
Esophagitis (LA Grade)	n=16	n=1	0.47
CLE Class/BE			0.75
Circumferential n(%)	15(31.9)	4(44.4)	
Tongue-like n(%)	17(36.2)	2(22.2)	
Isolated Islands n(%)	15(31.8)	3(33.3)	
CLE/BE Type			
Short Segment n (%)	29(61.7)	2(22.2)	0.27
Long Segment n(%)	3(6.4)	4(44.4)	0.005
Length of CLE/BE Mean±SD (cm)	1.81±0.59	3.0±1.76	0.009

toms ( $p=0.004$ ), long segment BE ( $p=0.005$ ) and its length ( $p=0.009$ ) were significant risk factors for BE (table 2).

## DISCUSSION

The global evidence-based consensus (i.e. Montreal definition of GERD)<sup>1</sup> has recommended that in population-based surveys, GERD should be defined as troublesome symptoms of heart burn and/or regurgitation. The mean±SD age of all recruited GERD patients was 48.15±10.90 years with 66.67% of patients being men and 33.33% being women. P. Sharma et al.<sup>9</sup> also reported a male predominance in patients with GERD in a study from Northern India.

Seventy-two percent of patients had no esophagitis on endoscopy (i.e. NERD) and 107 (28%) patients had erosive reflux disease with varying severity. Our results are consistent with studies from western community-based studies reporting 60-70% of patients having typical reflux symptoms, i.e. heart burn and/or regurgitation, without any esophageal mucosal injury on endoscopy.<sup>33</sup> The contribution of hiatus hernia in patients with GERD is controversial. Epidemiologic and physiologic data confirm the importance of hiatus hernia in patients with more severe esophagitis, peptic stricture and BE. We found that 40.47% of patients with GERD had hiatus hernia but only 54.21% of them had erosive esophagitis on endoscopy. Most studies on the prevalence of GERD are based on symptom-defined GERD according to the Montreal definition.<sup>1</sup> The prevalence of GERD in India is higher than previously estimated and seems to be between 8% to 19% which is comparable to GERD prevalence rates reported from western countries.<sup>8-10,34</sup>

The main objective of our study was to estimate the prevalence of BE among patients with GERD in India in the era when the prevalence of GERD has been reported to be increasing in our country. Previous studies from India have reported a prevalence rate between 2.6% to 23.64% in three different studies conducted until 2002.<sup>15-17</sup> Of the 378 patients with GERD in our study, there was an endoscopic suspicion of CLE in 56 patients. Therefore, we observed a prevalence rate of 14.81% of endoscopic BE in patients with GERD. The prevalence of endoscopically suspected short and long

segment BE in Asia is reported to be 5-7% and 1-3.4%, respectively.<sup>30,31</sup> In our study, the prevalence of endoscopically suspected short and long segment BE was 8.2% and 1.85%, respectively, consistent with the reported prevalence rates from other countries in Asia. Out of 56 patients only nine fulfilled the criteria for the diagnosis of BE (columnar lined mucosa with intestinal type goblet cells [SIM] on histological examination). So, the prevalence of histologically proven BE was 2.38% in patients with GERD (n=378). The prevalence of BE varies around the world and it seems to be higher in western countries than eastern counterparts. BE is typically found at an average age of 55 years with a male predominance which was also observed in our study. Nasseri-Moghaddam et al. found that GERD is common among Iranian patients referred for diagnostic endoscopy. The prevalence of SIM-GEJ among this population was comparable to what has been reported in Western countries.<sup>34</sup>

Therefore, even in the era of a reportedly increasing prevalence of GERD in India and other Asian countries, the rate of BE has still remained low. Previous studies from India have reported a prevalence rate of BE between 2.6% to 23.6%. The reason for this wide variation is the heterogeneity in selecting patients and varying criteria for defining BE. In 1997 Amarapurkar et al.<sup>17</sup> studied 150 cases of dyspepsia, four patients were detected as having SIM on histological examination of endoscopic biopsy specimens and 63 had gastric metaplasia. Four (2.6%) out of 150 patients with dyspepsia had BE which is almost similar to our results. Punia et al.<sup>16</sup> studied 55 patients with symptoms of GERD. In their study, 13 patients were diagnosed as having BE (6 detected as having SIM and 7 as gastric metaplasia) with a prevalence rate of 23.4%. Similarly, Dhawan et al.<sup>15</sup> reported a prevalence rate of 6% for BE in 271 patients with symptoms of GERD.

Five (15.15%) patients in the conventional group and four (17.39%) in the chromoendoscopy group were detected as having SIM on histological examinations. We found that both techniques were equally effective in identifying histological BE ( $p=0.55$ ).

The mean±SD number of biopsies per patient for detection of SIM was 4.12±1.70 in the conventional group and 3.0±0.78 in the chromoendoscopy group ( $p=0.002$ ). Therefore, on endoscopic suspicion of BE, fewer biopsies are needed to be taken from positively stained areas after MB chromoendoscopy as the probability of having SIM in positively stained specimens remains high. Similar results were obtained by Sharma et al.<sup>36</sup> who assessed the detection of SSBE after MB chromoendoscopy compared with conventional biopsy.

John et al.<sup>37</sup> reported that MB directed biopsy was similar to conventional biopsy in the detection of SIM and dysplasia which is consistent with our study. However, chromoendoscopy was more time consuming and had higher patient discomfort rates.<sup>37</sup> Chromoendoscopy was not recommended for endoscopic surveillance of patients with BE by Dave et al.<sup>38</sup> who also found that MB directed biopsies were neither sensitive nor specific for detecting SIM. Our results were similar to a meta-analysis involving 450 patients from 9 different studies<sup>39</sup> for assessing the diagnostic yield of MB chromoendoscopy for detecting SIM and dysplasia in BE. Only a comparable yield was achieved when evaluated against the conventional method. In contrast, a few studies have shown that MB chromoendoscopy is useful for detecting SIM in long segment BE but not in short segment BE and required fewer biopsies in patients suspected of having short segment BE. We observed that there was no difference in the detection of SIM in long segment BE by either of the two methods. But chromoendoscopy was helpful in detecting SIM in two patients with isolated islands of columnar appearing mucosa where as conventional was useful in one patient only.

The predictors of SIM were determined using logistic regression with univariate analysis. Male sex has been reported to be a risk factor for both BE and carcinoma of esophagus.<sup>40</sup> We also observed a male predominance in patients with SIM (88.88%) which was statistically insignificant ( $p=0.49$ ) when compared with patients without SIM. Age has been also considered a risk factor for BE in various stud-

ies from Asia. The mean±SD age of patients with SIM in our study was 52.56±8.84 years which is similar to the mean age at which diagnosis of BE is made. Similarly, a mean age of 51.5 to 66.7 years was reported in different studies from Asian countries.<sup>13,41</sup> The duration of symptoms before upper endoscopy in our study did not differ significantly on our study ( $p=0.46$ ), although a study by Lieberman et al.<sup>42</sup> showed increased risk of BE with increasing duration of GERD symptoms. The symptoms of reflux in our study was a good predictor of the risk for BE ( $p=0.004$ ) which was consistent with another study.<sup>43</sup> In our study the existence of hiatus hernia ( $p=0.16$ ) or its length ( $p=0.54$ ) did not differ significantly between the two groups. Avidan et al.<sup>44</sup> found increased risk of BE in patients with hiatus hernia and the size of hiatus hernia had a linear correlation with the length of BE.

Most of the patients in our study had grade A esophagitis in the group who had no SIM on histological examination and a single patient with SIM had LA-Grade B esophagitis ( $p=0.83$ ). So we did not find erosive esophagitis to be a predictor of BE which is contrary to a study carried out by Zhang et al.<sup>45</sup> The different morphological types of BE were not a risk factor for BE ( $p=0.75$ ). The length of CLE has been identified as a risk factor for SIM in different studies. Similar observations were made in our study. The mean±SD length of CLE was 3.0±1.26 cm in patients with SIM as compared with 1.8±0.59 cm in patients without SIM ( $p=0.001$ ). Okita et al.<sup>46</sup> also found that long segment BE was a predictor of SIM on histological examination. We did not find dysplasia in any of our patients who had SIM.

In conclusion, the prevalence rate of endoscopically suspected CLE in GERD patients was 14.81%. Also, the prevalence of endoscopically suspected short and long segment BE was 8.2% and 1.85%, respectively. The prevalence rate of histological BE (SIM) was 2.38% in patients with GERD in Northern India. The role of chromoendoscopy was not superior in terms of improved detection of SIM but was valuable in targeting the stained areas and taking fewer biopsy samples compared with the con-

ventional method. Moreover, reflux symptoms and long segment CLE and its length were significant risk factors for BE.

Most of the studies including ours observed that the majority of patients who had endoscopic suspicion of BE lack SIM when subsequent biopsy samples were taken. Studies should be conducted to determine endoscopic predictors, which can be taken as surrogate markers for histological BE and subsequently only patients with these predictors be subjected to biopsy.

### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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